

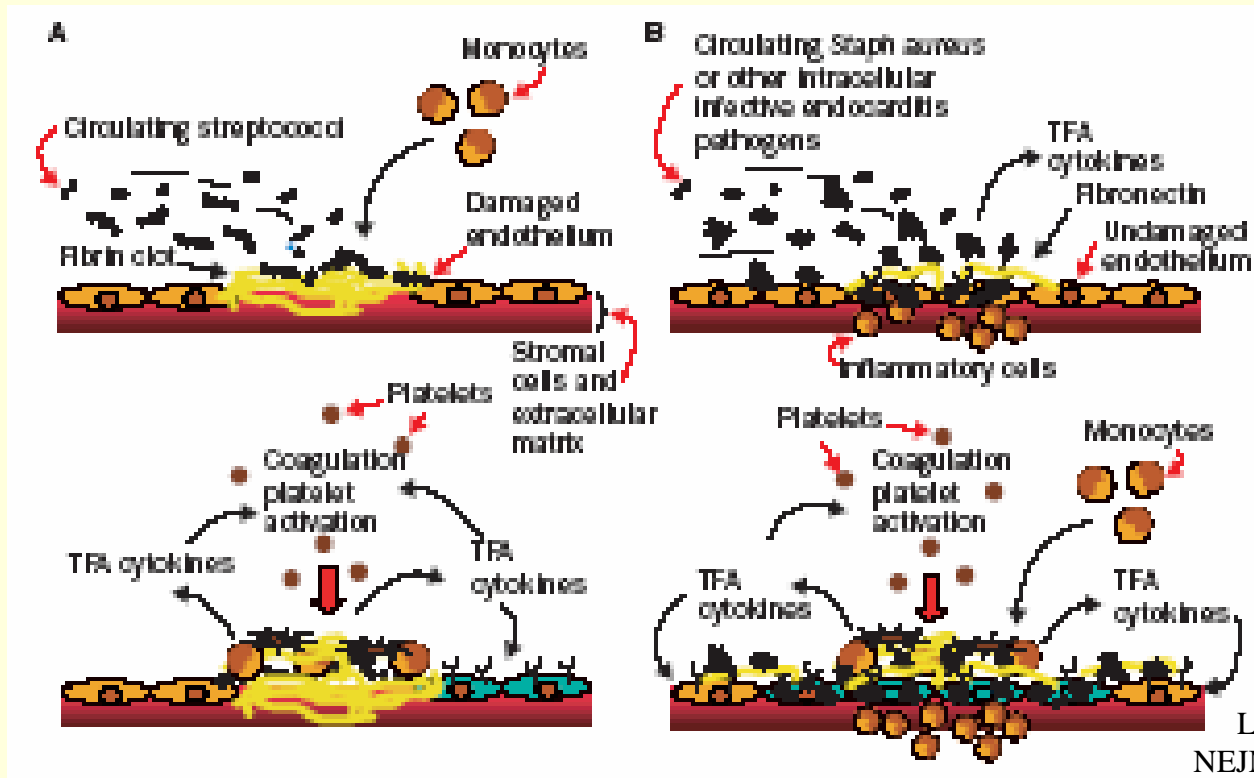


Infective Endocarditis: definition and epidemiology

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Definition

= a microbial infection of the endocardial surface (including large intrathoracic vessels and intracardiac foreign bodies)



Case definition

Gold standard = anatomopathologic or
autoptic confirmation

IE = syndrome diagnosis

: Integration of clinical, laboratory and
echocardiographic data permit diagnosis
in live patients

MODIFIED DUKES CRITERIA

Major criteria

1. Blood culture positive for IE

- 1) Typical microorganisms consistent with IE from 2 separate blood cultures:
 - Viridans streptococci, *Streptococcus bovis*, HACEK group, *Staphylococcus aureus*; or
 - Community-acquired enterococci, in the absence of a primary focus; or
- 2) Microorganisms consistent with IE from persistently positive blood cultures:
 - At least 2 positive cultures of blood samples drawn 12 h apart; or
 - All of 3 or a majority of >4 separate cultures of blood (with first and last sample drawn at least 1 h apart)
- 3) Single positive blood culture for *Coxiella burnetii* or antiphase I IgG antibody titer 1:800

2. Evidence of endocardial involvement

- 1) Echocardiogram positive for IE
 1. Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted
 2. material in the absence of an alternative anatomic explanation; or
 3. Abscess; or
 4. New partial dehiscence of prosthetic valve
- 2) New valvular regurgitation (worsening or changing of pre-existing murmur not sufficient)

Minor Criteria

- 1) **Predisposition** (predisposing heart disease or IV drug use)
- 2) **Fever** (temperature $> 38^{\circ}\text{C}$)
- 3) **Vascular phenomena** (major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway's lesions)
- 4) **Immunologic phenomena** (glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor)
- 5) **Microbiological evidence** (positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with IE)
- 6) **Echocardiographic minor criteria eliminated**

MODIFIED DUKES CRITERIA

Definite infective endocarditis

Pathologic criteria

- (1) Microorganisms demonstrated by culture or histologic examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or
- (2) Pathologic lesions; vegetation or intracardiac abscess confirmed by histologic examination showing active endocarditis

Clinical criteria^a

- (1) 2 major criteria; or
- (2) 1 major criterion and 3 minor criteria; or
- (3) 5 minor criteria

Possible infective endocarditis

- (1) 1 major criterion and 1 minor criterion; or
- (2) 3 minor criteria

Rejected

- (1) Firm alternate diagnosis explaining evidence of infective endocarditis; or
- (2) Resolution of infective endocarditis syndrome with antibiotic therapy for ≤ 4 days; or
- (3) No pathologic evidence of infective endocarditis at surgery or autopsy, with antibiotic therapy for ≤ 4 days; or
- (4) Does not meet criteria for possible infective endocarditis, as above

Validation of criteria on Dukes database:

- 99 % specificity
- 98 % negative predictive value
- On 286 surgical confirmed patients
: 74 % definite; 26 % possible; 0 % rejected

- Performance in culture negative IE ?
- High proportion of possible cases

Epidemiology

- Incidence

- For US and Western Europe
- 3.6/100.000/year (range 0.3-22.4)
(meta-analysis, 3784 ptn, 1993-2003)
- Male/female ratio 1.7/1

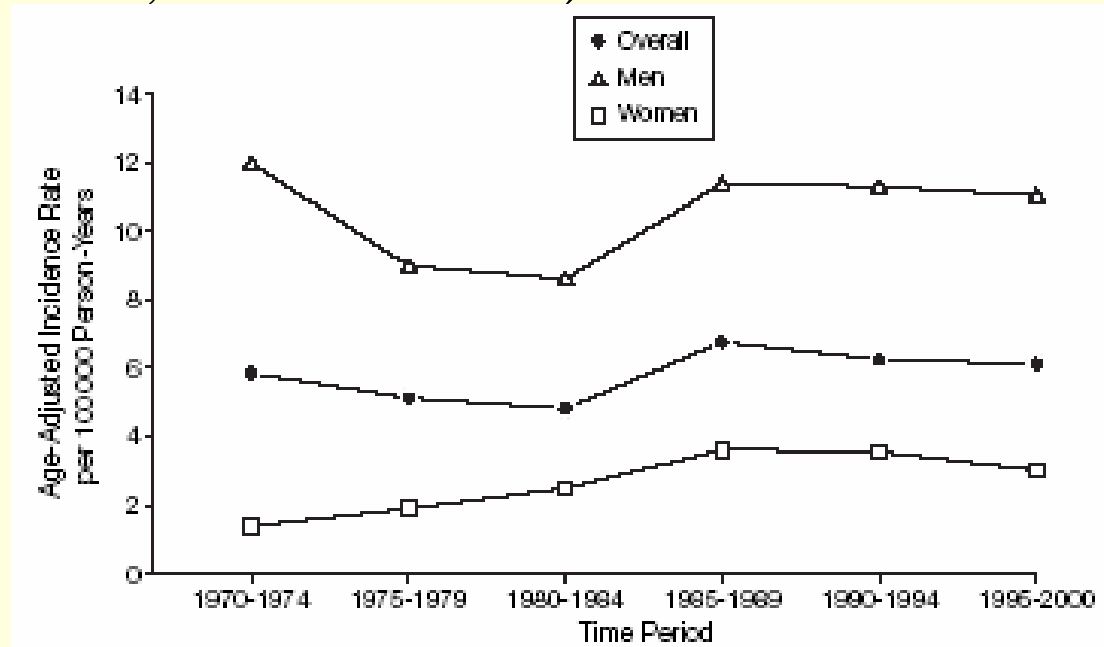
Lancet, 2004, 363, 139-49

NEJM, 2001, 345, 1318-1330

- No change in incidence over time
 - France survey (population of 16 million):
 - ✓ 1983: 2.4/100.000/y
 - ✓ 1991: 2.9/100.000/y
 - ✓ 1999: 2.6/100.000/y

JAMA, 2002, 288, 75-81

- Minnesota survey (30 year survey on 51.000 in 1970; 90.000 in 2000)

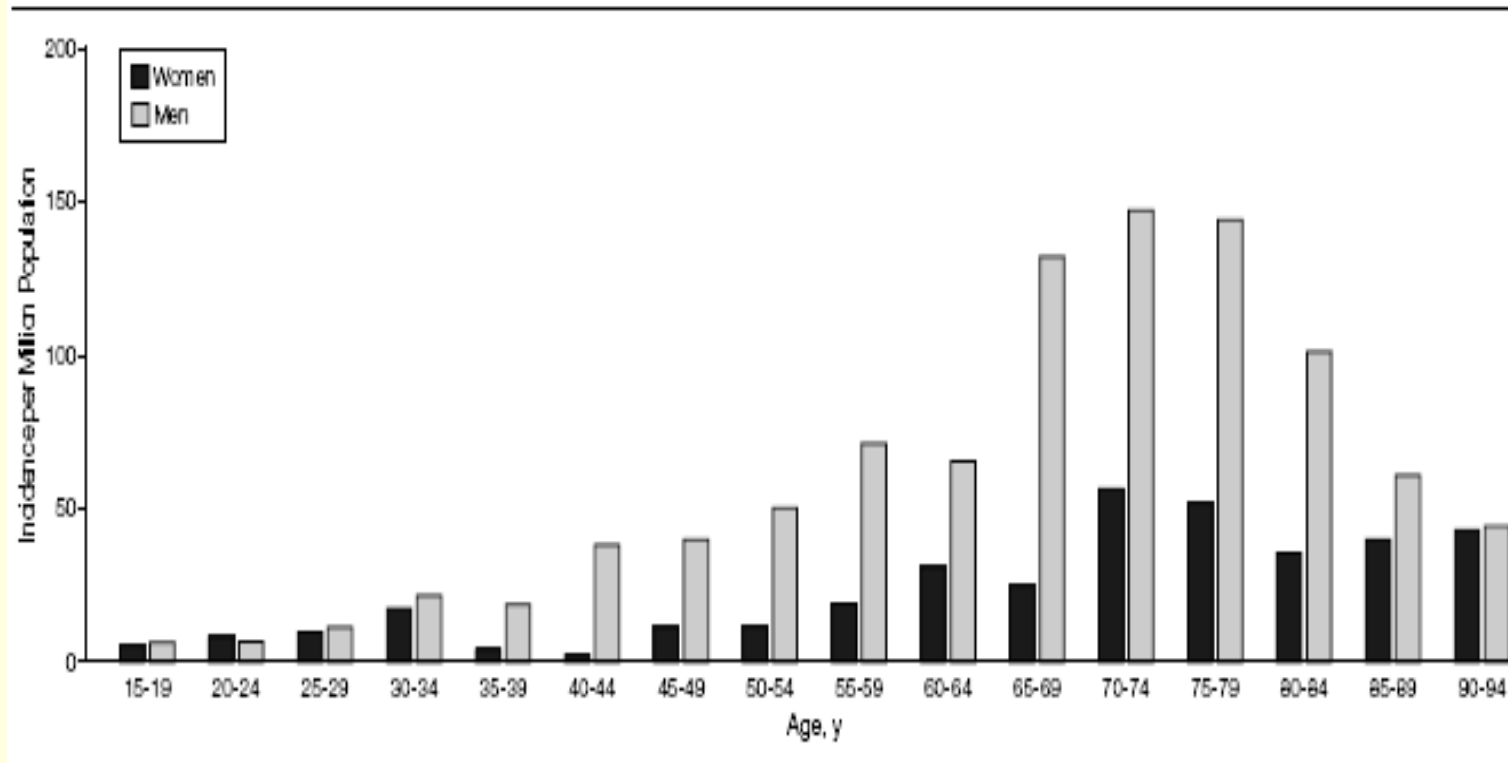


JAMA, 2005, 293, 3022-8

- Influence of age:

- Mean age 36-69 y
- Increasing incidence with increasing age

Figure. Incidence of Infective Endocarditis by Age and Sex in the Study Population



Lancet, 2004, 363, 139-49
JAMA, 2002, 288, 75-81

- Trend to increase in age of onset:

- ✓ 1926: < 30 year

- 1943: 39 year

- 2002: 58 year

Mandell, 2005, 975-1022

- ✓ Preantibiotic era: 30-40 year

- More recently: 47-69 year

NEJM, 2001, 345, 1318-1330

Real increase or change in case definition
and medical practice ???

- Location of IE:

- Depends on risk population

Table 2. Location of Infective Endocarditis (IE) in Patients (N = 390)

Location	No. (%)
Aortic valve	136 (35)
Mitral valve	112 (29)
Aortic and mitral valves	55 (14)
Tricuspid valve	37 (9)
Pulmonic valve	2 (1)
Bilateral IE	6 (2)
Pacemaker	18 (5)
With left-sided IE	5 (1)
Without left-sided IE	13 (4)
Undetermined*	24 (6)

*Nonoperated patients with lack of echocardiographic evidence of endocardial involvement (10 native valve disease, 7 valvular prosthesis, 6 without previously known heart disease, and 1 congenital heart disease).

Table 1. Demographic and Clinical Characteristics of Infective Endocarditis Cases (N = 107)

Characteristics	No. (%)
Demographic	
Age, mean (range), y	61.5 (18.8-90.6)
Women	29 (27)
Clinical	
Modified Duke classification	
Definite	94 (88)
Possible	13 (12)
Valve condition	
Native	84 (79)
Prosthetic	23 (21)
Valves involved*	
Aortic	36 (34)
Mitral	49 (46)
Aortic and mitral	12 (11)
Right-sided or bilateral	4 (4)
Unknown	8 (7)

- 80-90 % left heart IE

- **Risk factors**

1. Native-valve disease

- Decrease in rheumatic heart disease
- Increase in degenerative heart disease (> 50 % in patients > 60 y)
- mitral valve prolaps (100/100.000/year)?

2. IV drug use

- Incidence 150-2000/100.000/y
- Younger peoples (30-40 y)
- Tricuspid 50 %; aorta 25 %; mitral 20%
- 75 % *S. aureus*; mainly on healthy valves

3. *Prosthetic-valve (1-25 %)*

- Risk 1 % at 12 months, 2-3 % at 5 year
- Early (< 2 months) vs late (> 12 months)

4. *Nosocomial –acquired IE (7-29 %)*

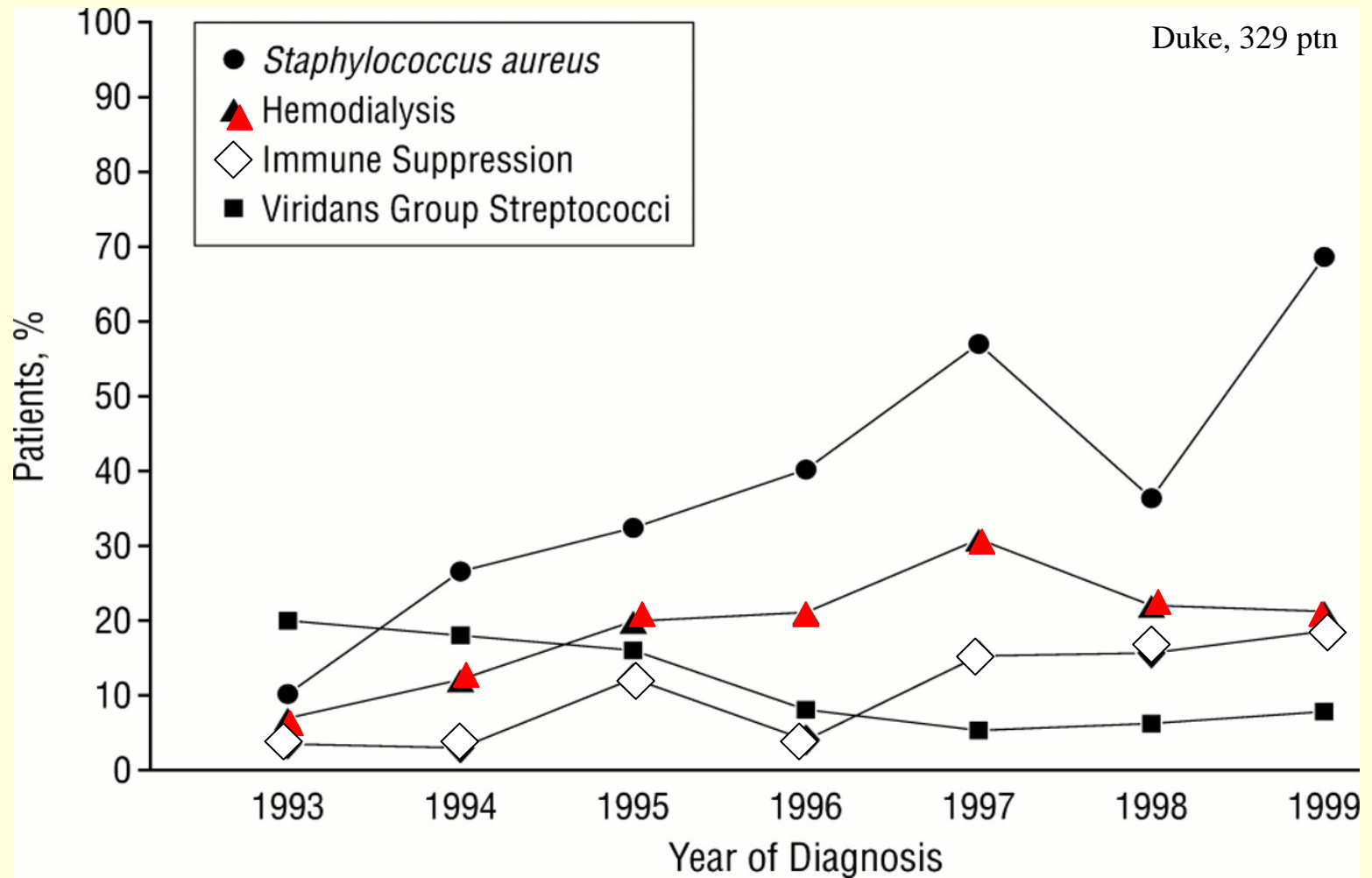
- Onset > 72 hours - up to 6 months
- RR for IE × 25 due to hospitalisation (27/100.000/year)
- invasive procedures; wound infections or situation with risk of bacteraemia (37%)
- > 50 % infected intravascular devices
- Case fatality 24 to > 50 %

Lancet, 2004, 363, 139-49
NEJM, 2001, 345, 1318-30
JAMA, 2002, 288, 75-81.
CID, 2004, 38, 843-50
CMI, 2006, 12, 5-12
Arch Int Med, 2002, 162, 90-4

5. Other risk factors

- Kidney disease/dialysis; diabetes; IV catheters; previous skin infections

Circulation, 2000, 102, 2842-8



Increase in risk factors for nosocomial IE ?

Table 1. Distribution of Underlying Heart Disease in Patients (N = 390) With Infective Endocarditis

	No. (%)
Native valve disease*	119 (31)
Left heart	112 (91)
Right heart	6 (5)
Both sides	1 (1)
Prosthetic valve	63 (16)
Congenital heart disease	4 (1)
Unspecified heart murmur	19 (5)
No previously known underlying heart disease	185 (47)

*Included within this group are 2 patients who had a history of valve repair without valve replacement.

Versus 22 % in 1975-83
 46 % in 1984-92

- Etiology

- Streptococci	27-54
- <i>Viridans streptococci</i> (11- 44)	
- <i>Other</i> (6-16)	
- Enterococci	6-8
- Staphylococci	29-42
- <i>S. aureus</i> (18-32)	
- <i>CoNS</i> (6-11)	
- HACEK	1-5
- Culture negative	1-18

JAMA, 2002, 288, 75-81
JAMA, 2005, 293, 3012-21
JAMA, 2005, 293, 3022-28
JCM, 2005, 43, 5238-42
CID, 2003, 36, 697-704

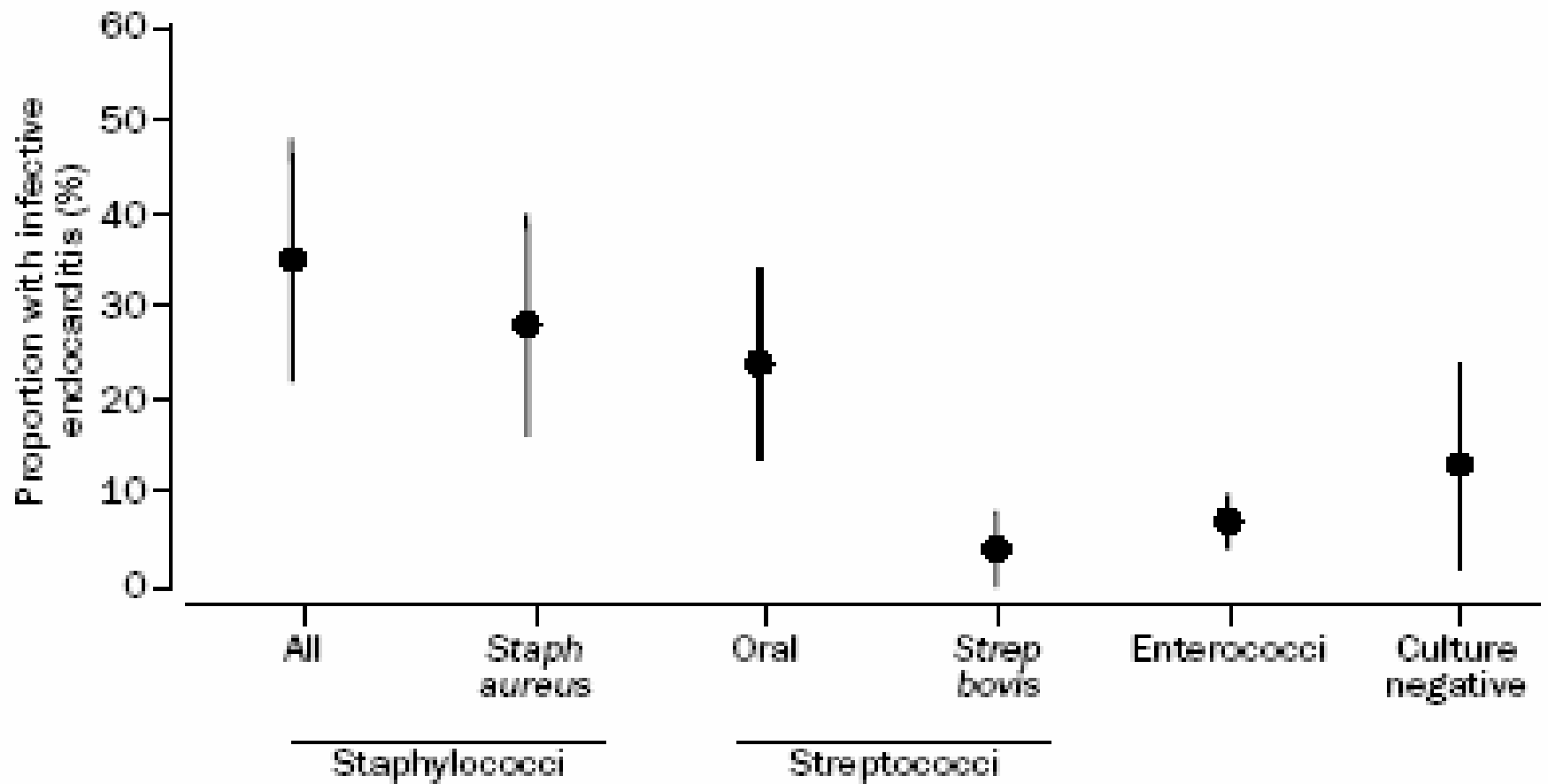


Figure 1: Microbial epidemiology of infective endocarditis

Upper graphs indicate proportion (mean [SD]) of specific pathogens responsible for infective endocarditis in 3784 episodes (webappendix references 1-26).

TABLE 1. MICROBIOLOGIC FEATURES OF NATIVE-VALVE AND PROSTHETIC-VALVE ENDOCARDITIS.

PATHOGEN	NATIVE-VALVE ENDOCARDITIS				PROSTHETIC-VALVE ENDOCARDITIS		
	NEONATES	2 MO–15 YR OF AGE	16–60 YR OF AGE	>60 YR OF AGE	EARLY (<60 DAYS AFTER PROCEDURE)	INTERMEDIATE (60 DAYS–12 MO AFTER PROCEDURE)	LATE (>12 MO AFTER PROCEDURE)
	approximate percentage of cases						
Streptococcus species	15–20	40–50	45–65	30–45	1	7–10	30–33
<i>Staphylococcus aureus</i>	40–50	22–27	30–40	25–30	20–24	10–15	15–20
Coagulase-negative staphylococci	8–12	4–7	4–8	3–5	30–35	30–35	10–12
Enterococcus species	<1	3–6	5–8	14–17	5–10	10–15	8–12
Gram-negative bacilli	8–12	4–6	4–10	5	10–15	2–4	4–7
Fungi	8–12	1–3	1–3	1–2	5–10	10–15	1
Culture-negative and HACEK organisms*	2–6	0–15	3–10	5	3–7	3–7	3–8
Diphtheroids	<1	<1	<1	<1	5–7	2–5	2–3
Polymicrobial	3–5	<1	1–2	1–3	2–4	4–7	3–7

*Patients whose blood cultures were rendered negative by prior antibiotic treatment are excluded. HACEK denotes haemophilus species (*Haemophilus parainfluenzae*, *H. aphrophilus*, and *H. paraphrophilus*), *Actinobacillus actinomycetemcomitans*, *Campylobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*.

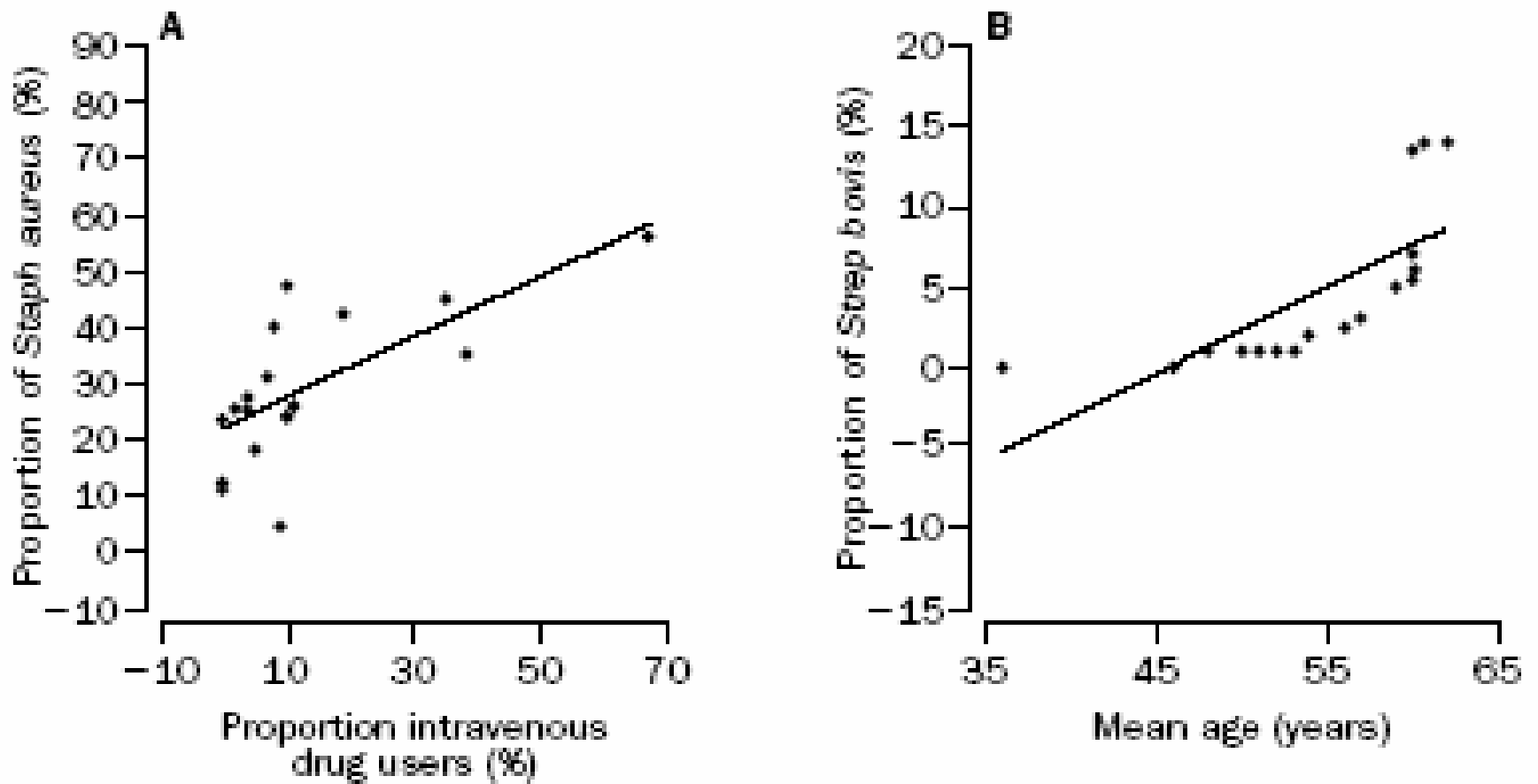
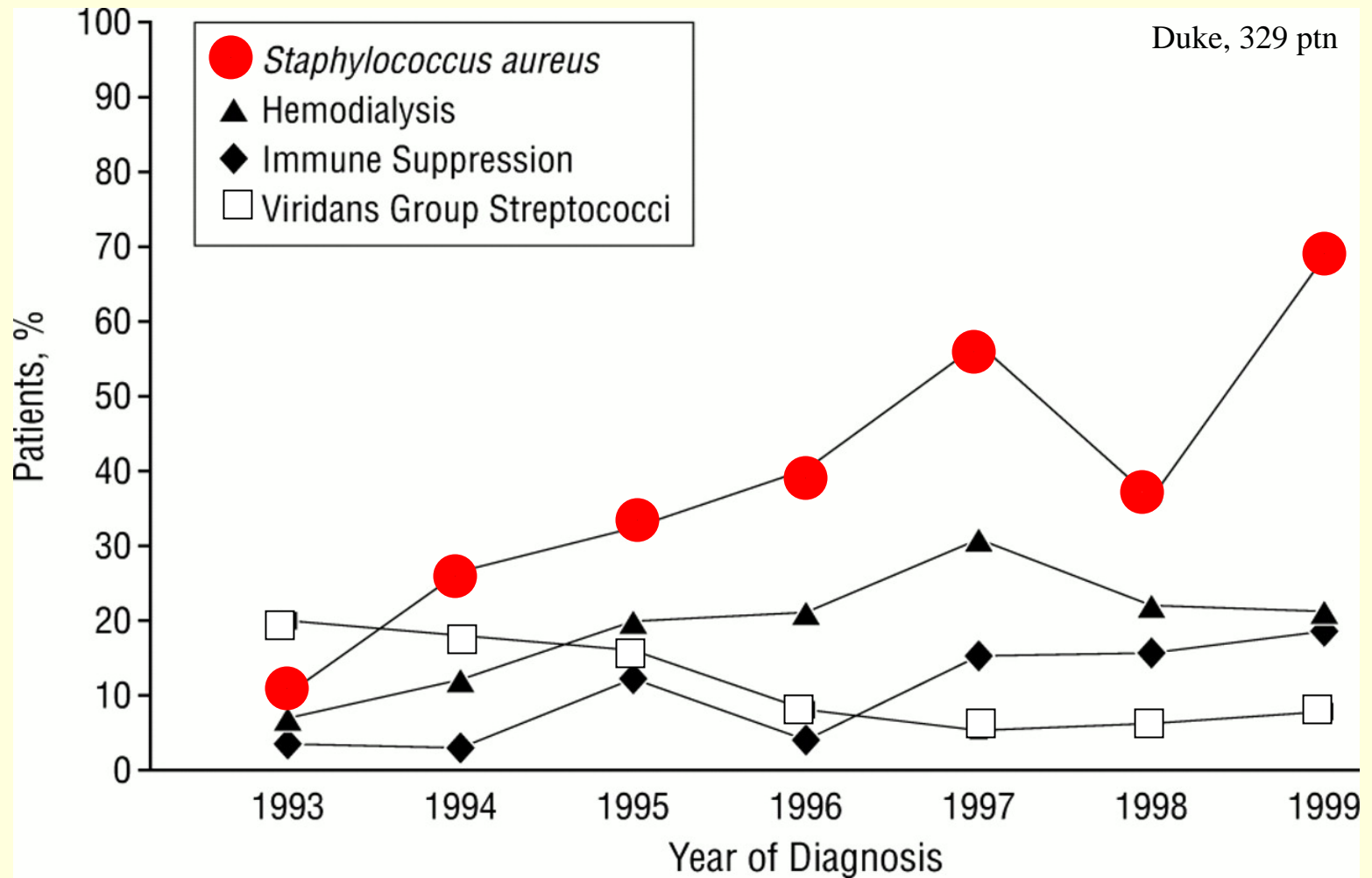


Figure 1: Microbial epidemiology of infective endocarditis

Lower two graphs present linear regressions between proportion of *Staph aureus* endocarditis and proportion of intravenous drug users (A; webappendix references 1, 2, 6-8, 10, 11, 13, 16, 17, 19-24, 26), and proportion of *Strep bovis* disease and mean age (B; webappendix references 1-3, 8, 10-20, 22, 23).



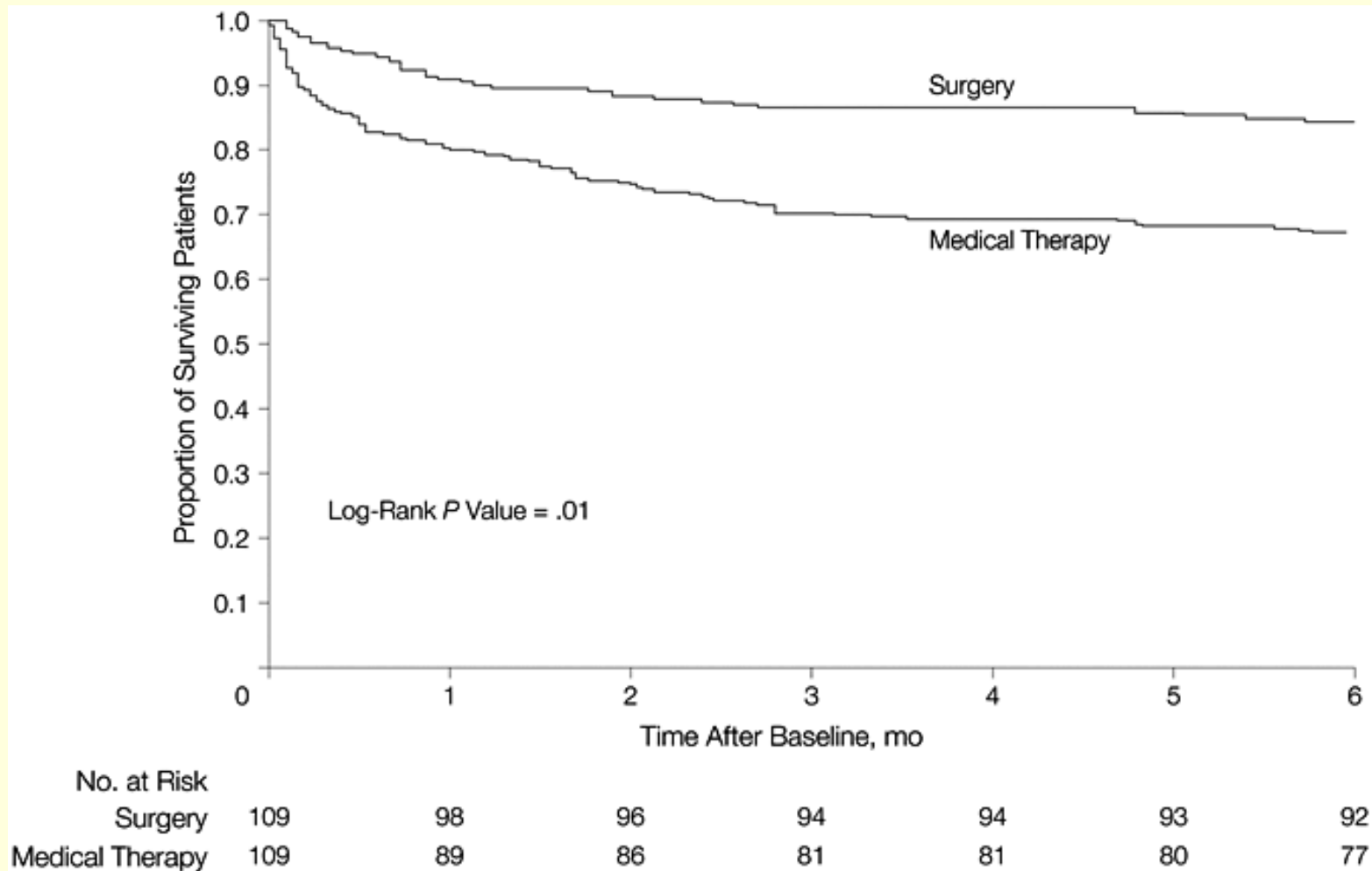
Increase *S.aureus*, decrease in viridans *Streptococci*

- Mortality:

- without antibiotics 100 %
- Global after 6 m 11-26 %
- 1. According to etiology
 - *Streptococcus* endocarditis 4-16 %
 - *Enterococcus* 15-25 %
 - *Staphylococcus aureus* endocarditis 25-47 %
 - Q fever 3-37 %
 - Fungal, pseudomonas, ... > 50 %
- 2. According to type of endocarditis
 - Right side endocarditis 10 %
 - Prosthetic valve endocarditis 29 %
 - Hospital acquired endocarditis 24-56 %
- 3. According to symptoms
- 4. According to therapy given (medical or combined)

NEJM, 2001, 345, 1318-30
CID, 2004, 38, 843-50
JAMA, 289, 1933-40

Kaplan-Meier Curve Relating Valve Surgery to Time to Death Among Propensity-Matched Patients



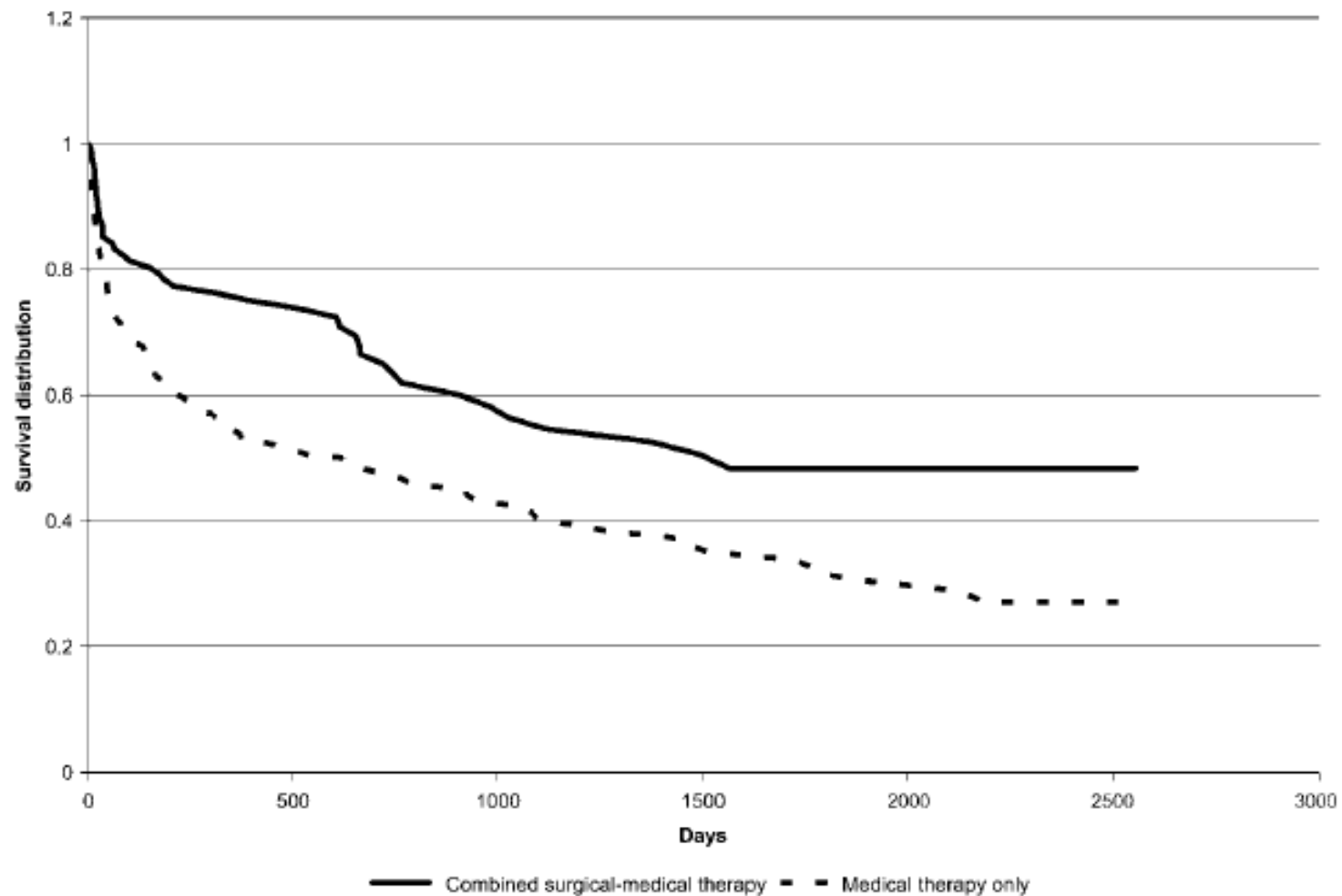


Figure 1. Unadjusted Kaplan-Meier survival curves of patients with infective endocarditis (IE) who received only medical therapy versus patients with IE who received surgical and medical therapy. At 6 months after treatment, 252 patients were considered to be at risk; at 1 year, 213 patients were at risk; at 2 years, 142 patients were at risk; at 3 years, 97 patients were at risk; at 4 years, 70 patients were at risk; and at 5 years, 40 patients were at risk.

Complication score: (cohort 513 cases)

1. Mental state		
alert		
lethargy/disorientation	RR 1,98	4
2. Charison comorbidity score		
0 – 1		
≥ 2	RR 1,76	3
3. Congestive heart failure		
none or mild		
moderate to severe	RR 1,91	3
4. Microbiology		
Viridans <i>streptococci</i>		
<i>S. aureus</i>	RR 3,56	6
Other	RR 4,87	8
5. Treatment		
Surgery		
Medical treatment	RR 2,45	5

Prognosis as a function of this score: (513 patients cohort)

Prognostic group					P-value
	1	2	3	4	
Points	≤ 6	7-11	12-15	> 15	
N° Patients	150	147	124	92	
6 month mortality N°	9	25	22	58	
%	6	17	31	63	< 0,001

Table 2. Five-year mortality characteristics of patients with left-side-associated infective endocarditis (IE).

Duke, 426 ptn

Characteristics	Patients who survived (n = 171)	Patients who died (n = 162)	P
Age, mean years ± SD	53.2 ± 26.1	62.6 ± 24.8	<.001
Sex			.152
Male	102 (59.7)	94 (51.9)	
Female	69 (40.4)	78 (48.2)	
Hemodialysis	20 (11.7)	63 (38.9)	<.001
Diabetes mellitus	39 (22.8)	65 (40.1)	<.001
HIV infection	2 (1.2)	9 (5.6)	.026
Cancer	14 (8.2)	34 (21.0)	<.001
Aortic valve IE	0 (0.0)	5 (3.1)	.003
Congenital heart disease	26 (15.2)	10 (6.2)	.009
Evidence of IE on index physical examination	139 (81.3)	150 (92.6)	.002
Blood microorganism			
No growth	28 (16.4)	11 (6.8)	.007
Staphylococcus aureus	46 (26.9)	77 (47.5)	<.001
Coagulase-negative staphylococci	15 (8.8)	23 (14.2)	.120
Viridans group streptococci	27 (15.8)	9 (5.6)	.003
Enterococcus species	19 (11.1)	19 (11.7)	.859
Other	36 (21.1)	23 (14.2)	.102
Surgery	55 (32.2)	23 (14.2)	<.001
Stroke	29 (16.4)	38 (23.5)	.106
CHF			
Class I	0 (0.0)	0 (0.0)	NA
Class II	6 (3.5)	2 (1.2)	.176
Class III	6 (3.5)	4 (2.5)	.579
Class IV	20 (11.7)	26 (16.0)	.250
Intracardiac abscess	29 (17.0)	23 (14.2)	.499
Blood sample culture results persistently positive for bacterial growth	19 (11.1)	48 (29.6)	<.001

Is the epidemiology changing ?

1. No change in incidence

2. Several changes in profile of the disease

1. Risk factors

↓ rheumatic heart disease

↑ degenerative heart disease, IV drug use, nosocomial IE, dialysis

↑ N° of patients without known predisposing factor

2. Increase in age of onset

3. Shift toward *S. aureus* (dialysis and nosocomial) and *Strep. bovis* (elderly)

4. Increase combined medical/surgical therapy; decrease mortality ???